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Mapping One Form of Autosomal Dominant Postaxial Polydactyly Type A to Chromosome 7p15-q11.23 by Linkage Analysis

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Summary

Postaxial polydactyly type-A (PAP-A) in humans is an autosomal dominant trait characterized by an extra digit in the ulnar and/or fibular side of the upper and/or lower extremities. The extra digit is well formed and articulates with the fifth, or extra, metacarpal/metatarsal, and thus it is usually functional. In order to map the gene responsible for PAP-A, we studied a five-generation Indian family of 37 individuals (15 of whom were affected). A genomewide search with highly informative polymorphic markers on part of the pedigree showed linkage between the PAP-A phenotype and markers on chromosome 7p15-q11.23 (no crossovers were found with D7S526, D7S795, D7S528, D7S521, D7S691, D7S667, D7S478, D7S1830, D7S803, D7S801, or ELN). The highest LOD score was obtained with marker D7S801 (Z_{max} = 4.21; θ = 0). Haplotype analysis enabled the mapping of the PAP-A phenotype in this family between markers D7S2848 and D7S669. Analysis of additional families with PAP-A will narrow down the critical genomic region, facilitate positional cloning of the PAP-A gene, and/or uncover potential genetic heterogeneity.

Introduction

Postaxial polydactyly (MIM 174200) in humans is an autosomal dominant trait characterized by the presence of an extra finger and/or toe on the ulnar or fibular side of the hands and feet, respectively. Morphologically, there exist two different types: In postaxial polydactyly type A (PAP-A), the extra digit is rather well developed, articulates with the fifth, or extra, metacarpal/metatarsal, and is usually functional. In postaxial polydactyly type B (pedunculated postminimus), the extra digit is not well formed and is frequently in the form of a skin tag (Temtamy and McKusick 1969). The penetrance of type B has been estimated to be ~65% (Scott-Emuakpor and Madueke 1976), while that of type A is much higher (Temtamy and McKusick 1969; Castilla et al. 1973). Types A and B sometimes occur in the same pedigree (Sverdrup 1922; Odiorne 1943; Ventruto et al. 1980; Kucheria et al. 1981). The occurrence of postaxial polydactyly in the general population varies among different racial groups and is ~10 times more frequent in Blacks than in Caucasians (Frazier 1960). In Caucasians living in the United States, incidence figures vary from 1/3,300 to 1/630 live births and in African Americans from 1/300 to 1/100 live births (Temtamy 1990). Postaxial polydactyly has also been reported as an autosomal recessive trait (Mohan 1969; Cantu et al. 1974; Mollica et al. 1978) and in association with various syndromes (Merlob et al. 1981). Among the chromosomal abnormalities, postaxial polydactyly occurs in ~75% of cases with trisomy 13 (in particular 13q31-q34) (Lewandowski and Yunis 1977).

The loci for a few other human polydactylies have been mapped. These include the synpolydactyly type II on chromosome 2q31 (Sarfarazi et al. 1995), complex bilateral polysyndactyly and triphalangeal thumb on 7q36 (Heutink et al. 1994; Tsukurov et al. 1994; Hing et al. 1995; Radhakrishna et al. 1996), Greig cephalopolysyndactyly on 7p13 (Brueton et al. 1988), and Ellis-van Creveld syndrome on 4p16 (Polymeropoulos et al. 1996). Positional cloning and candidate gene analysis experiments revealed that the gene responsible for the Greig cephalopolysyndactyly is *GLI3* (Vortkamp et al. 1991), and that for synpolydactyly type II is *HOXD13* (Muragaki et al. 1996).

In order to map the locus associated with the PAP-A trait, we performed a genomewide search with genotypes of microsatellite polymorphic markers in members of the Indian family UR004. Markers within chromosome 7p15-q11.23 showed no recombination with the phenotype. The highest LOD score was obtained with D7S801 (Z_{max} = 4.21; θ = 0).

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Subjects and Methods

Family UR004

We studied an Indian family, UR004, with PAP-A, from the Gujarat state in the western part of India (partial pedigree is shown in fig. 1). This five-generation pedigree consists of a total of 37 individuals, with 6 affected males and 9 affected females with PAP. Figure 2 shows this trait and radiograms in selected individuals. All 11 affected individuals examined showed extra postaxial digits in both hands and feet (12 fingers and 12 toes). These extra digits were well developed and similar

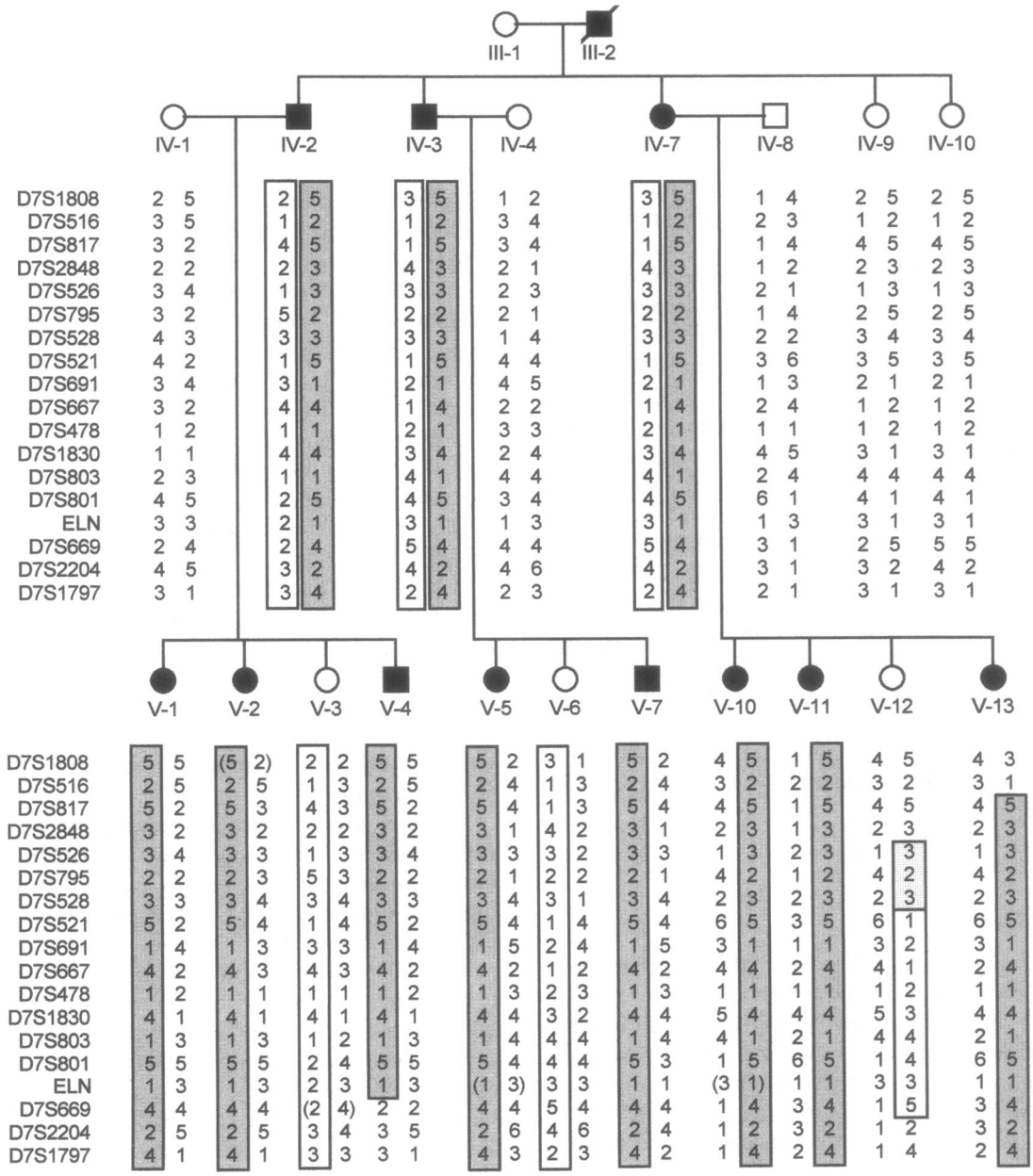

Figure 1 Partial pedigree of family UR004 with postaxial polydactyly (PAP-A). Only individuals studied are shown. Genotypes for selected polymorphic microsatellite markers on chromosome 7p15-q11.23 are shown. The order of the markers from top to bottom (from 7pter to 7qter) is that determined in the linkage maps of CHLC and Généthon (see text). The order of pairs of markers D7S817/D7S2848 and D7S2204/D7S1797 could not be determined and is arbitrarily shown. Blackened symbols = individuals with polydactyly; empty symbols = unaffected individuals. Haplotypes of polymorphic markers could not be determined for individuals IV-9 and IV-10, because their parental genotypes were unknown. The phenotype-related haplotype is shown within a gray box; the "normal" haplotype is shown within an empty box. In individual V-12, recombination for markers in the lighter box could not be determined, because of parental homozygosity. The phase of genotypes in parenthesis could not be determined, because of parental heterozygosity for the same alleles.

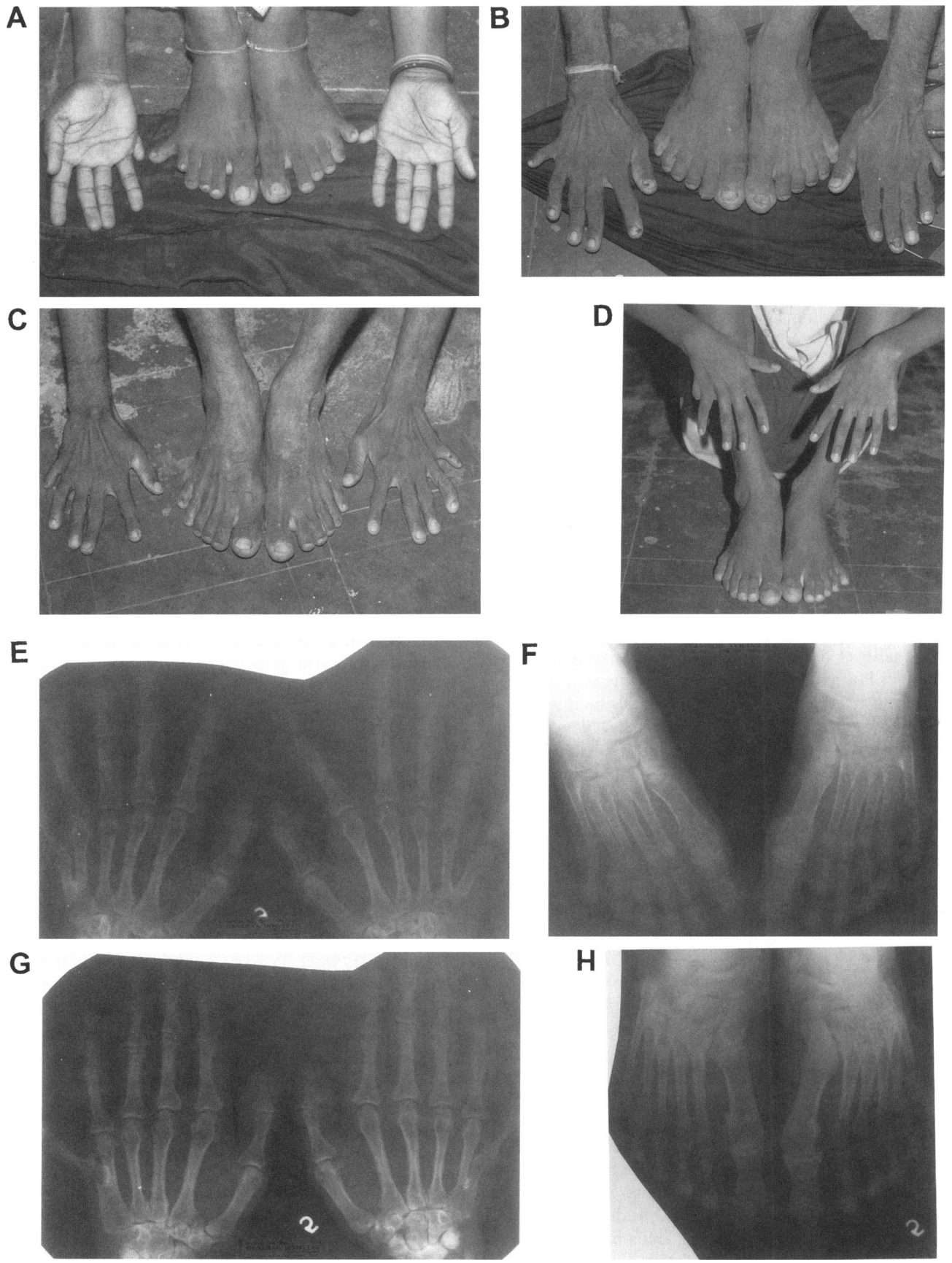

Figure 2 *A–D*, Clinical photographs of hands and feet of four affected individuals of pedigree UR004, showing the bilateral postaxial polydactyly type A. *E–H*, X-rays of hands and feet of different individuals.

to the normal fingers/toes. There was no other associated anomaly in this family; in addition, only one individual (V-13) showed syndactyly of the extra digit and fifth finger in one hand. The pedigree clearly indicated an autosomal dominant mode of inheritance with apparently full penetrance; no skipping of any generation was observed in the extended pedigree. The postaxial polydactyly trait was not disadvantageous in the majority of the affected individuals; however, surgical corrections were done in some affected females, because of social problems. None of the individuals in the pedigree had any cranial or dental anomaly.

Blood samples were collected from 19 consenting individuals including 11 affected and 8 normal individuals. Clinical photographs were taken from all affecteds included in the linkage study. Hand and foot X-ray radiographs were taken from selected individuals.

DNA Polymorphism and Linkage Analysis

Genomic DNA was purified from peripheral blood lymphocytes according to the standard SDS-proteinase-K and phenol/chloroform extraction method (Sambrook et al. 1989). DNA polymorphisms were analyzed by PCR amplification of short sequence repeats. These markers were selected from the Généthon and CHLC collections (NIH/CEPH Collaborative Mapping Group 1992; Buetow et al. 1994; Gyapay et al. 1994; Dib et al. 1996) and obtained from Research Genetics Human Screening microsatellite set and Eurogentec custom oligonucleotide synthesis facilities. One oligonucleotide primer of each marker was labeled with γ^{32}P-ATP with T4 polynucleotide kinase. PCR was performed on a MJ Research PTC-100 and Biometra UNO I thermocyclers to amplify from 90 ng of genomic individual DNA in a total volume of 15 μl mixture per reaction containing 0.4 pM of labeled forward primer, 2.6 pM of unlabeled reverse primer, 1.3 μM of each dNTP, and 0.25 U *Taq* polymerase (Pharmacia). PCR products were separated by electrophoresis in a 6% denaturing urea/polyacrylamide gel (Blouin et al. 1995). Genotypes were scored after autoradiography.

Family information and marker genotypes were stored in the pedigree computer program Cyrillic (Cherwell). Analysis was performed using the ILINK, MLINK, and LINKMAP programs of LINKAGE version 5.2 (Lathrop et al. 1984) and FASTLINK version 3.0 (Cottingham et al. 1993) software packages. Multipoint linkage analysis was performed with the help of the computer facility of the U.K. Human Genome Mapping Project resource center (http://www.hgmp.mrc.ac.uk/). Maximum LOD and location scores were calculated for each marker locus by assuming autosomal dominant mode of inheritance with ≤100% of penetrance. For all polymorphic markers, the allele frequencies were kept equal.

Results

A genomewide search using highly informative polymorphic markers was performed on DNA from the members of the UR004 pedigree with PAP-A. Polymorphisms on chromosomes 2q31 and 7q36, the sites of synpolydactyly type II and polysyndactyly with triphalangeal thumb (Tsukurov et al. 1994; Heutink et al. 1994; Sarfarazi et al. 1995), were first used but showed no evidence for linkage. A total of 45 polymorphic markers were then used, until the identification of the first marker on chromosome 7p11-p13 (D7S1830) that showed no recombination with the phenotype. Subsequently, only markers on chromosome 7 were used. Results of two-point pairwise analyses between the phenotype of PAP-A in family UR004 and chromosome 7 markers at various recombination fractions and 100% penetrance are shown in table 1. A maximum two-point LOD score of 4.21 was obtained for D7S801 at recombination fraction $\theta = 0$. The corresponding LOD scores for the marker D7S801 for penetrances of 90%, 80%, 70%, 60%, and 50% were 4.01, 3.82, 3.64, 3.48, and 3.33, respectively. No recombination was also observed with polymorphic markers D7S526, D7S795, D7S528, D7S521, D7S691, D7S667, D7S478, D7S1830, D7S803, and ELN. However, recombination was observed between the phenotype and markers D7S1808, D7S516, D7S817, D7S2848, D7S669, D7S2204, and D7S1797. The order of all markers used on chromosome 7 was taken from the linkage maps of Généthon and the CHLC collection (NIH/CEPH Collaborative Mapping Group 1992; Buetow et al. 1994; Gyapay et al. 1994; Dib et al. 1996). Haplotype analysis revealed that the interval of no recombination, and therefore the most likely genomic interval of the PAP-A locus in family UR004, was between markers D7S2848 on 7p15 to D7S669 on 7q11.23 (fig. 3).

Multipoint linkage analysis was also performed using markers on chromosome 7. An example with markers D7S2848, D7S667, D7S801, and D7S1797 is shown in figure 4. The map distances used in this multipoint linkage analysis were D7S2848–24.3 cM–D7S667–10.1 cM–D7S801–17.4 cM–D7S1797 and were taken from the CHLC map version 4 (http://www.chlc.org:80/data/CHLCmaps/). A maximum multipoint LOD score of 4.21 was obtained at $\theta = 0$ cM from marker D7S801. The maximum multipoint LOD score was approximately the same regardless of the combinations of markers used in the analysis. Linkage and haplotype analysis therefore indicated that the mapping position of the PAP-A locus in family UR004 was in the interval between D7S2848 and D7S669 on chromosome 7p15-q11.23.

Table 1

Pairwise Two-Point LOD Scores between the PAP-A Phenotype in Family UR004 and Several Chromosome 7p15-q11.23 Polymorphic Markers at Various Recombination Fractions and 100% Penetrance

	LOD Score at θ =											
Marker	0	.001	.01	.05	.1	.2	.3	.4	Z_{max}	θ	CHLC[a] (cM)	MIT[b] (cM)
D7S1808	−∞	−3.41	−1.44	−.19	.24	.46	.38	.16	.463	.221	0	48
D7S516	−∞	−3.09	−1.12	.12	.52	.68	.54	.23	.684	.191	0	48
D7S817	−∞	−.11	.85	1.37	1.45	1.27	.89	.39	1.449	.095	...	...
D7S2848	−∞	−.09	.87	1.39	1.47	1.28	.90	.39	1.460	.092	5.3	...
D7S526	1.07	1.06	1.04	.95	.82	.58	.32	.10	1.065	0	8.5	57
D7S795	1.05	1.04	1.02	.93	.81	.56	.32	.10	1.046	0	11.6	57
D7S528	.90	.90	.88	.80	.69	.48	.26	.08	.903	0	19.3	65
D7S521	3.17	3.17	3.11	2.88	2.58	1.97	1.31	.58	3.173	0	24.5	70
D7S691	2.89	2.89	2.84	2.65	2.40	1.87	1.26	.55	2.892	0	25.2	72
D7S667	3.01	3.00	2.96	2.74	2.46	1.85	1.16	.42	3.010	0	29.6	76
D7S478	1.91	1.91	1.88	1.73	1.53	1.12	.69	.24	1.913	0	31.3	78
D7S1830	3.01	3.01	2.96	2.74	2.46	1.85	1.16	.42	3.010	0	35.8	82
D7S803	2.71	2.70	2.66	2.44	2.16	1.55	.88	.25	2.709	0	37.7	...
D7S801	4.21	4.21	4.14	3.86	3.48	2.66	1.74	.72	4.214	0	39.7	...
ELN	2.33	2.33	2.29	2.14	1.93	1.48	.98	.40	2.333	0	48.8	...
D7S669	−∞	.91	1.85	2.30	2.27	1.86	1.23	.47	2.310	.066	55.0	105
D7S2204	−∞	−3.13	−1.17	.07	.48	.65	.52	.22	.655	.193	...	...
D7S1797	−∞	−1.79	.15	1.30	1.57	1.46	1.01	.39	1.596	.125	57.1	108

Note.—Maximum LOD scores for marker D7S801, using other penetrance values, are cited in the text. The order of the majority of markers from 7pter to 7qter is as determined in the CHLC version 4 and Généthon linkage maps. The order of marker pairs D7S817, D7S2848 and D7S2204, and D7S1797 could not be determined and is arbitrarily shown.

[a] Distances from marker D7S1808 as determined in the CHLC sex-averaged linkage map version 4 (http://www.chlc.org:80/data/CHLCmaps/).

[b] Distances (sex-averaged) from the most-7pter marker as given in the MIT/Whithead human genome mapping center (http://www.genome.wi.mit.edu/).

Discussion

Linkage analysis of the PAP-A phenotype in an Indian family (UR004) showed that the locus for this autosomal dominant trait cosegregated with DNA polymorphic markers on 7p15-q11.23 in this family. Markers showing no recombination with the PAP-A phenotype span a chromosomal region of ~45 cM on 7p15-q11.23. The marker with the highest maximum LOD score (Z_{max} = 4.21) for θ = 0 was D7S801. Haplotype analysis revealed that the mapping interval for the PAP-A locus in this family is between marker D7S2848 on 7p15 and D7S669 on 7q11.23, since recombination events have been observed with these markers in two affected individuals (V-4 and V-13) and one unaffected individual (V-12) (fig. 1). In the event that individual V-12 is a nonpenetrant carrier of the affected locus, the 7p distal border of the mapping interval extends to marker D7S516. The penetrance used for the results of table 1 in the Indian family UR004 was 100% on the basis of inspection of the pedigree. The maximum LOD score for the most informative marker, D7S801, remained >3, even with penetrance of 50%. Until the PAP-A gene is identified, it is impossible to demonstrate unequivocally that PAP-A is completely penetrant in the Indian family UR004. In PAP-B, in which the extra digit is not well formed and is frequently in the form of a skin tag (pedunculated postminimi) and shows autosomal dominant inheritance, the penetrance is markedly reduced (Walker 1961). Families with both types of postaxial polydactyly, types A and B, have been described elsewhere (Ventruto et al. 1980; Kucheria et al. 1981). Since the family reported here showed the presence of the PAP-A phenotype only, it did not provide an answer to the proposed hypothesis that both PAP-A and PAP-B are due to mutations in the same locus. In addition, linkage analysis in more families with PAP-A is needed to study a potential genetic heterogeneity of this condition. Family UR004 studied here showed PAP-A in both hands and feet; it is therefore unknown whether the loci in families with PAP-A of hands or feet only map to the same genomic interval as in family UR004.

The genomic area described here showing linkage to the PAP-A trait in family UR004 is on the same chromosomal arm as the *HOXA* gene cluster and contains the *GLI3* gene. The gene products of the *HOXA* gene cluster are implicated in determining the body plan and limb development (Duboule 1994; Cohn and Tickle 1996). However, it is unlikely that a member of the *HOXA* gene family is the gene for the PAP-A in family UR004,

because linkage analysis showed recombination events between the phenotype and markers D7S1808, D7S516, D7S817, and D7S2848 (individuals V-12 and V-13 of fig. 1). Since all of these markers map proximal to *HOXA* (Murray et al. 1994; Borrow et al. 1996), we concluded that the *HOXA* gene cluster is not responsible for the phenotype.

No recombination was observed between the PAP-A phenotype of family UR004 and markers flanking the zinc finger–containing gene *GLI3* (i.e., between D7S691 and D7S478 on 7p13 [Tsui et al. 1995]). Mutations in the *GLI3* gene (deletions due to translocations) were associated with the Greig cephalopolysyndactyly (Kruger et al. 1989; Vortkamp et al. 1991). This syndrome is characterized by preaxial polydactyly of the feet, postaxial polydactyly of the hands, syndactylies of hands and feet, and mild craniofacial anomalies such as slight hypertelorism and a high prominent forehead (Merlob et al. 1981). The human *GLI3* gene contains ⩾14 exons that are spread over 280 kb of genomic DNA (Vortkamp et al. 1995). In

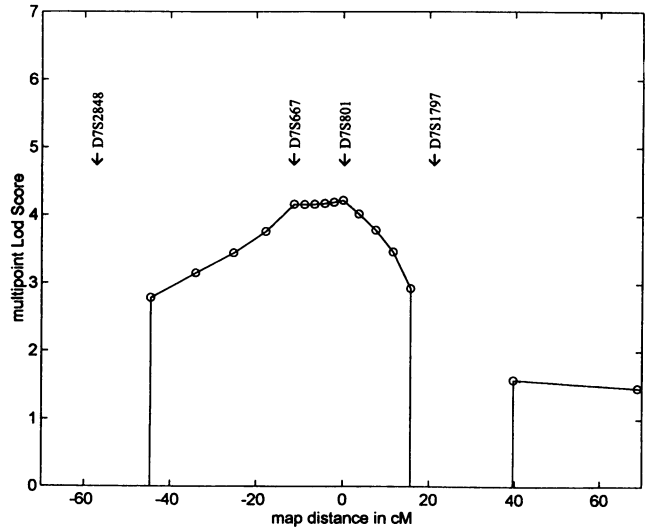

Figure 4 Multipoint linkage analysis between the PAP-A phenotype and four selected chromosome 7 markers (D7S2848-D7S667-D7S801-D7S1797). The location of marker D7S801 was set at map position zero. The map distances were calculated using the Haldane mapping function.

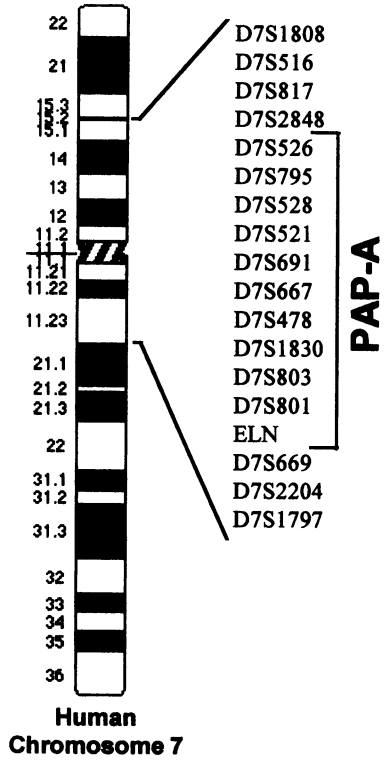

Figure 3 Schematic representation of human chromosome 7. The cytogenetic localization of short-sequence repeat polymorphic markers linked to the PAP-A trait are indicated for the region 7p15-q11.23. The bracket indicates the region of no detectable recombination of the PAP-A phenotype with the polymorphic markers shown. The position of the *GLI3* candidate gene (see text) is between markers D7S691 and D7S478 on 7p13. The order of pairs of markers D7S817, D7S2848 and D7S2204, and D7S1797 could not be determined and is arbitrarily shown.

the mouse mutant "extra toes" (*Xt*), a deletion of the 5′ part of the murine *Gli3* gene has been identified (Vortkamp et al. 1992; Hui and Joyner 1993). In another mouse mutant, "anterior digit deformity" (*add*), the expression of *Gli3* appears to be reduced as a result of a transgene integration in presumed regulatory elements upstream of the *Gli3* coding sequence (Hui and Joyner 1993). The human *GLI3* gene is therefore a candidate gene for the PAP-A phenotype in family UR004. Mutation analysis in DNAs of members of the UR004 family needs to be performed to rule out the involvement of the *GLI3* gene in PAP-A.

There are a number of human malformation syndromes with postaxial polydactyly as part of their clinical picture. The OMIM catalog (http://www3.ncbi.nlm.nih.gov/omim/) gives 73 entries (seach of October 4, 1996) for the "postaxial polydactyly" query. The loci for some of these syndromes do not map in the chromosome 7 region described here, suggesting that several other loci are associated with postaxial polydactyly. For example, the locus for Ellis-Van Creveld syndrome (six-fingered dwarfism; MIM 225500) has been recently assigned by linkage analysis to chromosome 4p16 (Polymeropoulos et al. 1996). Similarly, several mouse mutants have been described with extra toes. Besides the two mentioned above, *Xt* and *add* associated with abnormalities of the *Gli3* gene on mouse chromosome 13, there is an unmapped mutant *Po* (postaxial polydactyly) (Nakamura et al. 1962); the relation of this mouse mutant with the human trait described here is unknown.

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